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SOME ASPECTS OF THE MECHANISM OF ANTIPHLOGENIC ACTION OF THE PHYTOCOMPOSITION "LESBOHOL"

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Abstract; Some mechanisms of the anti-inflammatory action of Lesbohol were studied in experimental animals. It was found that cyclooxygenase inhibition does not play a decisive role in the mechanism of the anti-inflammatory action of Lesbohol. Removal of the adrenal glands clearly reduces the anti-inflammatory activity of Lesbohol associated with the suppression of glucocorticoid secretion. Lesbohol suppresses the level of pro-inflammatory cytokines (IL-1-β and TNF-α) and increases the level of anti-inflammatory cytokine (IL-10). Suppression of the kinin system and a decrease in vascular permeability are important factors in the anti-inflammatory action of Lesbohol. It is believed that the mechanism of anti-inflammatory activity of Lesbohol is largely due to its antioxidant property.

Key words: phytocomposition, vascular permeability, kinin system, cyclooxygenases, pro- and anti-inflammatory cytokines, free radical processes.

Conflict of interest. The authors declare no obvious or potential interests related to the publication of this article.

Introduction

A mixture of dry plant extracts - Lesbohol exhibits high anti-phlogogenic activity in the model of aseptic inflammation induced by various flagogens [1-3]. Along with this, Lesbohol suppresses the proliferative phase of inflammation [4]. In the mechanism of anti-phlogogenic action of non-steroidal anti-inflammatory drugs (NSAIDs), as is known, the leading place is occupied by inhibition of cyclooxygenase (COX) activity [5,6]. Prostaglandins (PG) in the body of mammals are formed with the participation of COX from arachidonic acid performing a number of physiological functions (thrombus formation, vasoconstriction, increased platelet aggregation, increased blood flow in the kidneys, vasoconstriction, stimulation of the myometrium, fever, pain, inflammation). At the same time, suppression of COX activity by reducing the formation of PG E2 in the gastric mucosa inhibits its barrier function, which causes the development of gastropathy (ulcers, erosions) [7, 8]. This circumstance is one of the main factors leading to the cessation of pharmacotherapy with NSAIDs [9]. Based on this, an important problem of pharmacology is the development and implementation of new anti-inflammatory drugs with a different mechanism of action. In this regard, the phytocomposition Lesbohol consisting of a mixture of extracts of medicinal plants is of particular interest: large-leaved mediazia (Mediazia macrophylla), naked licorice (Glycirhiza glabra L.), rough St. John's wort (Hipericum scabrum L.) and ziziphora pedicellata (Ziziphora pedicellata Pazij Vved.), characterized by high anti-inflammatory activity and low toxicity [10]. However, the mechanism of anti-

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flagogenic activity of this phyto composition remains insufficiently studied. The above circumstance determined the objectives of the present study.

The aim of the present work was to study the influence of the Lesbohol phytocomposition on various pathogenetic links in the development of inflammation.

Materials and methods of the study

The experimental studies were conducted on mature white male rats of herd breeding weighing 160-180 g obtained from the nursery of the Department of Sanitary and Epidemiological Surveillance of the Main Medical Department under the Administration of the President of the Republic of Uzbekistan. Before inclusion in the experiment, the rats were kept in quarantine conditions for 14 days. During the quarantine period, all animals were examined, weighed, their age, motor activity and skin condition were taken into account. During the experiments, the animals were placed in 6 individuals in macrolon cages with a volume of 55x45x15 cm, under controlled vivarium conditions: air temperature 22 ± 2 ° C, relative humidity 60 ± 5%, bedding made of sawdust, in a well-ventilated room and day/night light mode. The animals were divided into experimental and control groups of 6 individuals each. The daily feed requirement was calculated taking into account the age of the animals. The experiments were conducted in accordance with the "Rules for laboratory work involving experimental animals" and the rules given in the European Convention for the Protection of Vertebrate Animals used for Experimental Research and other Scientific Purposes (ETS No. 123) Strasbourg 18.03.1986.

The effect of Lesbohol on the enzymatic activity of cyclooxygenase -1 (COX-1) and cyclooxygenase -2 (COX-2) was studied using a commercially available test system COX inhibitory screening assay kit (Cayman Chemicals, USA). The test system was used to directly estimate the amount of prostaglandin F2α (PGF2α) formed during the reduction of PGH2 induced by tin chloride (SnCl2), a product of the interaction of cyclooxygenase (enzyme) and arachidonic acid (substrate). The amount of PGF2α was estimated by ELISA. The method is based on competitive binding of PGF2α (prostaglandins present in samples, control and standards) and PGF2α–acetylcholinesterase (AChE) conjugate (PGF2α-tracer) with specific monoclonal antibodies [11].

The adrenalectomy model was performed on rats in compliance with the rules of asepsis and antisepsis [12]. For this purpose, in animals under ethaminal anesthesia (40 mg/kg), a 1.5-2 cm long incision was made in the soft tissues below the 12th rib on both sides along the depilated area along the spine. The adrenal glands were removed together with the connective tissue strand, grasped with tweezers. The soft tissues and skin were sutured layer by layer. After the operation, the animals received a 1% sodium chloride solution instead of drinking water. On the eighth day after the operation, 1 hour after the administration of Lesbohol at a dose of 50 mg/kg, a 6% dextran solution in a volume of 0.1 ml was subplantarly injected into the hind paw and the course of aseptic inflammation was studied. The volume of the animals' paws was measured using a digital plethysmometer (Ugo Basile Srl, Italy) before and 60, 120, 180 and 240 minutes after the administration of dextran. The anti-inflammatory activity of the drug was judged by the difference in the volume of the paws before the start of the experiments and at the time of maximum development of edema. The value of anti-inflammatory activity (PVA) of the drugs was calculated using the formula:

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ПВА=Vкон-Vоп/Vкон x 100 = %, where

Vcon - average increase in limb volume in the control cm3,Vop - average increase in limb volume in the experiment cm3. The study of the effect of Lesbohol (at a dose of 50 mg / kg) on the content of cytokines in the blood was carried out on the model of carrageenan inflammation in sexually mature laboratory animals. Groups of 6 individuals were formed in each. After the introduction of 1% carrageenan solution (Sigma-Aldrich, USA) into the hind paw, after 3 hours under light ether anesthesia, the animals were decapitated and blood was collected, in which the concentration of interleukins IL-10, IL-1β and TNF-α in the blood serum was determined by the method of solid-phase enzyme immunoassay (commercial ELISA kits manufactured by Human Diagnostics and Vector-Best, Russia).

The effect of Lesbohol on vascular permeability was studied according to the method of K.N. Monakova [10]. For these purposes, the animals were fixed with their backs on special machines and a 10 x 15 cm (150 cm2) area of the abdominal skin was cleared of hair. One hour after the administration of Lesbohol (at a dose of 50 mg/kg), a 1% solution of trypan blue was injected into the marginal vein of the rabbits' ear at a rate of 2 ml/kg of body weight. After 5, 30 and 60 minutes, 0.2 ml of xylene was applied with a micropipette to two symmetrical areas of the abdominal skin. The results were assessed by the difference in the time of appearance of the blue spot at the sites of xylene application in the control and experimental groups of animals. The effect of Lesbohol on the activity of the blood kinin system was studied using the method of G.S. Paskhina [10] on sexually mature white rats and Chinchilla rabbits. The rats were injected intraperitoneally with a sodium ethaminal solution at a dose of 40 mg/kg, then blood was taken from the femoral vein into a special siliconized test tube and centrifuged. To activate the kinin system, 0.1 ml of blood serum was taken into a clean siliconized test tube and 0.9 ml of isotonic sodium chloride solution was added. The resulting mixture in a ratio of 1:10 had the highest kinin activity. By adding the appropriate volume of physiological solution to it, dilutions of 1:20, 1:60, 1:180, 1:240, etc. were obtained. The activity of the blood kinin system was assessed by the highest degree of serum dilution, an intradermal injection of 0.1 ml of which still caused skin staining within 20 minutes from the moment of injection. Lesbohol at a dose of 50 mg/kg was administered orally 2 hours before blood sampling. Acute toxic hepatitis (ATH) was reproduced by subcutaneous administration of a 50% oil solution of tetrachloromethane in olive oil at a rate of 0.5 ml / 100 g. body weight for 4 days [13]. 1 hour after the introduction of hepatotoxin, the animals were divided into several groups, which were intragastrically administered a freshly prepared aqueous solution of Lesbohol at a dose of 50 mg / kg intragastrically. The control group of rats received a similar volume of water orally and olive oil subcutaneously. 24 hours after the last administration of drugs and hepatotoxin, the animals were decapitated under light anesthesia, blood was collected to determine the content of lipid peroxidation products: acyl hydroperoxides (AcGP) and malondialdehyde (MDA) [14]. The results of the studies were statistically processed using the Biostat 2009 software package using the variation statistics method with an assessment of the significance of the M±m characteristics and differences in the samples under consideration using Student's t-test. Differences in the compared groups were considered reliable at a significance level of 95% ($p<0.05$).

Results of the study and their discussion.

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Since the main mediator of the inflammatory process, as indicated, is PG [15], it can be assumed that the anti-inflammatory effect of Lesbohol is associated with the inhibition of cyclooxygenase (COX). Studies conducted in this regard have shown that the addition of Lesbohol in various concentrations to the incubation mixture did not lead to a change in the concentration of PGF2α - the final result of the interaction of the enzyme with arachidonic acid. Thus, from the data in Table 1 it is clear that under the influence of indomethacin, the formation of PGF2α is significantly reduced, which is manifested in the inhibition of COX-1 by 89.5%. The same direction, but a slightly stronger effect, was found by us when studying the effect of indomethacin on the activity of COX-2, where the inhibition of the formation of PGF2α was 98.9%.

Table 1

Results of interaction of indomethacin with different isoforms of cyclooxygenase

Sample (concentration in reaction mixture)	Concentration of PG F2α, ng/ml	% enzyme inhibition
Control 1 (COX-1)	248 ± 15	0
Indomethacin, 1.0 μg/ml (2.8 μM)	26 ± 3	89,5
Control 2 (COX-2)	6891 ± 738	0
Indomethacin, 1.0 μg/ml (2.8 μM)	74 ± 10	98,9

Therefore, indomethacin, as a non-selective COX inhibitor, showed high activity in in vitro experiments with COX-1 and COX-2 enzyme preparations, which is consistent with literature data [16,17]. We subsequently conducted studies on the interaction of Lesbohol with the COX-2 enzyme. As can be seen from the data in Table 2, Lesbohol does not have a significant effect on the formation of PGF2α. Thus, if in the control samples the concentration of PGF2α is 7142 ± 952 ng/ml, then in the samples containing Lesbohol the level of PGF2α does not undergo statistically significant changes.

Table 2

Results of the interaction of the Lesbohol substance with COX-2 enzymes

sample	Lesbohol concentration in the reaction mixture, μg/ml	PGF2α concentration taking into account sample dilution, ng/ml	% reduction in prostaglandin PGF2α
control	0	7142 ± 952	0
Lesbohol	0,1	7039 ± 866	1,4 ± 0,1
	1,0	6948 ± 711	2,7 ± 0,2
	2,0	6911 ± 673	3,2 ± 0,2
	5,0	6808 ± 702	4,6 ± 0,5

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Therefore, in the mechanism of the anti-inflammatory action of Lesbohol, the inhibition of COX activity does not play a pathogenetic role. Taking this circumstance into account, we conducted studies to establish other possible mechanisms of the anti-inflammatory activity of Lexbachol. The adrenal glands play an important role in the implementation of the anti-flagogenic effect of drugs that have the property of stimulating the production of glucocorticoids with pronounced anti-inflammatory activity [18,19]. In terms of establishing the mechanism of the anti-inflammatory action of Lesbohol, it is important to evaluate its effectiveness in animals with adrenalectomy (AE). The results of experimental studies have shown that adrenalectomy (AE) does not have a noticeable effect on the intensity of the exudation process. From the data in Table 3, it is clear that if in rats under the influence of dextran the volume of paws increased by 126.1% after 1 hour, then in AE rats it is 128.7%. i.e. AE does not have a noticeable effect on the development of the exudation process caused by dextran. In contrast, in AE rats treated with Lesbohol, the development of exudation was somewhat greater, which led to a decrease in the PVA of the drug. Thus, if after subplantar administration of dextran in AE rats, the average increase in paw volume relative to the initial value was 80.2%, then in AE rats previously treated with Lesbohol, it was 92.2%. These changes led to a decrease in the PVA value of Lesbohol to 25.9%, versus 37.1% in rats without adrenalectomy. The data presented indicate that the adrenal glands play some role in the mechanism of PVA of Lesbohol.

Table 3

The effect of Lesbohol on the course of aseptic arthritis induced by dextran in rats with adrenalectomy (M±m, n=6)

Groups	Dose, mg/kg	Group Dossier, mg/kg		Average increase in rat paw volume relative to baseline		PVA, in %
		source	in 1 hour	$см^3$	в %	
Intact						
control	-	0,92 ± 0,04	2,08 ± 0,10*	1,16 ± 0,12	126,1	-
Lesbohol	50	0,91 ± 0,03	1,64 ± 0,10*	0,73 ± 0,08	80,2	37,1
A d r e n a l e c t o m e n t						
control	-	0,87 ± 0,03	1,99 ± 0,09*	1,12 ± 0,10	128,7	-
Lesbohol	50	0,90 ± 0,02	1,73 ± 0,05*	0,83 ± 0,07	92,2	25,9

Note: * - statistically significant difference compared to baseline.

The role of IL-10 and IL-1β cytokines is to systemically regulate the response to inflammation, and the study of the indices of these substances in the study of the anti-inflammatory effects of new drugs is interesting and indicative in terms of establishing the signaling pathways of the effect of drugs on the inhibition of the inflammatory response [20-22]. Tumor necrosis factor is a key cytokine of the immune system. TNF-α regulates many biological processes, including proliferation, differentiation and death of various cells,

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inflammatory reactions, innate and acquired immunity, as well as the formation of the structure of various organs and tissues, including secondary lymphoid organs [23,24]. TNF-α is produced in response to various stimuli by immune cells, including monocytes, macrophages, dendritic cells, T and B lymphocytes, mast cells, as well as cells of the stroma, nervous system, skin and endothelium. Activated cells synthesize TNF-α as a transmembrane protein, which is later separated from the cell surface by metalloproteases, the main one of which is TNF-α-converting enzyme, and secreted as a soluble protein [25]. Based on this, in the next series of experiments, we studied the levels of interleukins 10, 1β and TNF-α in the peripheral blood of rats after treatment with Lesbochol under conditions of induced inflammation. Depending on the nature of the effect on the inflammatory process, cytokines are divided into pro-inflammatory, participating in the initiation of inflammation, and anti-inflammatory. The key pro-inflammatory cytokine is IL-1β, the main anti-inflammatory is IL-10 [26,27]. IL-10 is the most important anti-inflammatory cytokine, exerting mainly anti-inflammatory and anti-cytokine effects [28]. The sources of IL-10 are T-helper-2 lymphocytes (Th2), B-lymphocytes, monocytes/macrophages, keratinocytes, mast cells, thymocytes, a subpopulation of T-lymphocytes with suppressor activity - T-regulators 1. Macrophages produce IL-10 under the influence of exogenous and endogenous factors, such as endotoxins, catecholamines, etc. [29].

Table 4

Effect of Lesbohol on the content of interleukins IL-1-β, IL-10 and tumor necrosis factor alpha in the peripheral blood of rats

Groups	IL-1-β, pg/ml	IL-10, pg/ml	c IL-10, pg/ml
Preventive action (administration of drugs 1-14 days of the experiment)			
Intact	2,54±0,08	3,74±0,10	1,13±0,09
Control	13,80±0,40*	2,75±0,27*	4,87±0,11*
Lesbohol	5,97±0,42$^{*,\#}$	4,11±0,19$^{\#}$	2,27±0,14$^{*,\#}$
Therapeutic effect (administration of drugs 15-28 days of the experiment)			
Intact	2,54±0,08	3,74±0,10	1,13±0,09
Control	12,57±0,91*	2,14±0,18*	5,03±0,37*
Lesbohol	5,22±0,38$^{*,\#}$	4,37±0,28$^{*,\#}$	2,03±0,16$^{*,\#}$

Note: *- statistically significant difference in relation to intact (P<0.05), #- statistically significant difference in relation to control (P<0.05).

The results of the studies conducted in this regard allowed us to establish that the level of IL-1β cytokine in the control group rats was increased by 5.4 times, and the level of IL-10, on the contrary, was low - by 26.5% compared to intact (healthy) animals. At the same time, the data on the values of IL-1β concentrations in the group receiving Lesbohol were high by almost 2.35 times compared to healthy animals, but were low by 56.7% compared to the control. The concentration of IL-10 in rats receiving Lesbohol increased compared to the control to 4.11 ± 0.19 pg / ml. Consequently, the determination of biologically active

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inflammation markers (cytokines IL-1 β, IL-10 and TNF-α) allowed us to state the completion of the adaptive phase of the body in response to inflammation, which was expressed in the normalization of the levels of cytokines IL-1 β, IL-10 and TNF-α. In our study, the level of TNF-α in animals with inflammation (control group) was significantly higher compared to the same indicator in intact animals. In the experimental group receiving Lesbohol, the TNF-α value decreased to 2.27 ± 0.14 pg / ml.

Summarizing the obtained research results, we can conclude that rats with aseptic arthritis have a significant increase in the content of IL-1 β and TNF-α in the peripheral blood, which was accompanied by a statistically significant decrease in the level of IL-10.

Thus, the analysis of the results of the conducted studies on the study of PVA Lesbohol showed that aseptic inflammation leads to significant changes in the level of important inflammation mediators such as IL-1 β, IL-10 and TNF-α, and the use of Lesbohol to a sufficiently high degree eliminates the identified disturbances in the content of the studied cytokines.

As is known, inflammation is a typical pathological process that occurs under the influence of various pathogenic factors of infectious and non-infectious nature and is characterized by the development of a typical complex of vascular and tissue changes. Vascular changes are manifested in the zone of acute inflammation in the form of a sequential change in vascular spasm, arterial and venous hyperemia with the development of prestasis and stasis [30]. The results of this series of experiments showed that in control rabbits after the introduction of trypan blue, the appearance of skin staining developed at 5.21 ± 0.057 minutes five minutes after the application of xylene, and at 5.12 ± 0.049 and 5.17 ± 0.042 minutes after 30 and 60 minutes, respectively. In contrast, in rabbits preventively treated with Lesbochol, the appearance of a blue spot at five minutes after the introduction of trypan blue was equal to 6.70 ± 0.058, and at 30 and 60 minutes, respectively, 7.98 ± 0.077 and 8.81 ± 0.073 minutes. It is evident that the appearance of staining at the site of xylene application at different times from the beginning of the experiment developed statistically significantly later than in the controls. These results indicate a decrease in vascular permeability under the influence of Lesbochol. The kinin system is especially important for the regulation of inflammatory reactions, since bradykinin increases vascular permeability and causes vasodilation of arteries and veins of the intestine, aorta, uterus and urethra [14,31]. One of the components of the kinin system is bradykinin, which is considered one of the important mediators of inflammation.

The results of the studies showed that the serum of control animals, even at a dilution of 1:50,000, caused skin staining, while the serum of animals receiving Lesbohol required lower dilutions of blood serum (in a ratio of 1:160) to develop a similar color.

Consequently, the results of experimental studies allow us to state that Lesbohol clearly inhibits the kinin system.

This effect of the drug is probably due to the suppression of free-radical processes that play an important role in the development of many diseases. This conclusion is based on the results of separate series of experiments, which established a decrease in the content of malonic dialdehyde in the blood of rats under the influence of Lesbohol. The mechanism of

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damaging action of many pathogenic agents is based on increased formation of free radicals, which have a detrimental effect on the structure of biological membranes of cells and their organelles. This largely concerns tetrachloromethane, alcohol, etc. The level of lipid peroxidation, developing with increased formation of free radicals, is judged by the formation of MDA [32-34]. Since Lesbohol, like LIV-52, eliminates cytolysis phenomena, restores detoxifying, protein-forming and other functions of the liver [35], it is logical to assume that it suppresses the intensity of free radical processes, i.e. has an antioxidant effect. We studied the effect of Lesbohol on the content of AcGP and MDA in the blood serum in acute toxic hepatitis (ATH).

As shown by biochemical studies, the OTG caused by tetrachloromethane is accompanied by an almost twofold increase in the content of AcGP and MDA in the blood, which is consistent with the data of other researchers [35], and confirms the pathogenetic role of free-radical oxidation in the development of toxic hepatitis under the influence of tetrachloromethane. In contrast, in animals treated with Lesbohol, the level of MDA in the blood serum decreases by 44.0%. It is evident that the drug suppresses the intensity of free-radical oxidation of lipids. Therefore, it can be assumed that Lesbohol has a depressing effect on the intensity of free-radical processes during intoxication with hepatotoxins, which allows us to classify these drugs as antioxidants. There is reason to believe that it is precisely these properties of these drugs that underlie their favorable restorative effect on the functional state of biological membranes and inhibition of the formation of arachidonic acid, a precursor of cyclic endoperoxides and, accordingly, prostaglandins, an important mediator of inflammation.

CONCLUSIONS

1. In the mechanism of the anti-inflammatory action of Lesbohol, inhibition of cyclooxygenase does not play a decisive role.
2. Adnenalectomy clearly reduces the anti-inflammatory activity of Lesbohol associated with the suppression of glucocorticoid secretion.
3. Lesbohol suppresses the level of pro-inflammatory cytokines (IL-1-β and TNF-α) and increases the level of anti-inflammatory cytokine (IL-10).
4. Suppression of the activity of the kinin system and a decrease in vascular permeability are important factors in the anti-inflammatory action of Lesbohol.
5. The mechanism of anti-inflammatory activity of Lesbohol is largely due to its antioxidant property.

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